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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,167	12/27/2001	David Botstein	P2930R1C10	7373

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EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,167	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-28, 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/23/03 and 4/29/03

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112 – Written Description

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 27-28 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification due to the use of the "hybridization" language. The use of the "hybridization" language causes the claims to include variants for which no written description is provided in the specification since there is no description of any other sequences besides SEQ ID NO: 7 which "hybridize" to SEQ ID NO: 7. The

specification has express possession of only one sequence, SEQ ID NO: 7, in a genus which comprises hundreds of trillions of different possibilities.

A central element in the utility guidelines and in the caselaw is whether there is substantial variation among the species in the broader genus which would share the inventive features of the disclosed sequence. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided. Further, these claims encompass alternately spliced versions of the proteins, allelic variants including insertions and mutations, inactive precursor proteins which have a removable amino terminal end, and only specific amino acid sequences have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

So while Example 9 of the utility guidelines reads stringent hybridization conditions as yielding less variation, the variation in the current case is significant because there is no expectation that other sequences which hybridize to SEQ ID NO: 7 would themselves hybridize to targets which are overexpressed in cancer cells, which is the asserted utility of SEQ ID NO: 7. One central problem with the current claims is that the while such variants of SEQ ID NO: 7 are likely to exist, there is a complete absence of knowledge on the part of applicant as to what sequence comprises these variants.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the claimed sequences using the "hybridization" language lacks any specific required structure. This is precisely the situation of naming a type of material which is generally known to likely exist, but, except for SEQ ID NO: 7 itself, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to anything which hybridizes to SEQ ID NO: 7 under stringent conditions.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than SEQ ID NO: 7. There is no conception of sequences which "hybridize" to SEQ ID NO: 7 except by the functional utility of "hybridization." Applicant has no definition of the structure of these molecules or of any structural element relating to these molecules whatsoever. The entire claim is functionally drawn to claim compounds which Applicant does not have, which Applicant has not made and which comprise specific sequences that Applicant does not know. These claims therefore fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Response to Arguments

3. Applicant's arguments filed August 24, 2004 have been fully considered but they are not persuasive.

The first issue is whether the claims comply with the written description requirement of 35 U.S.C. 112, first paragraph. In this analysis, Applicant does not focus on the legal framework, as enunciated in Lilly, which underlies the written description analysis for nucleic acids. Applicant fails to recognize that a structure function relationship is required by the Federal Circuit in Lilly to support a generic claim under the written description requirement. Appellant also fails to note that a "representative

number of species" is required. This is considered by the USPTO written description guidelines which note that in an unpredictable art, a single species is not sufficient to describe the genus.

It is the absence of any structure function relationship and the absence of a representative number of species which supports the conclusion that there is insufficient descriptive support for the current claims. This argument rests on three grounds. First, the single sequence that is actually described is not representative of the genus of any sequence which hybridizes under the stated conditions. Second, the claims entirely lack a structure function relationship since no function whatsoever is given for the nucleic acid sequences. .

Absence of a representative number of species

In the current case, the first question is what constitutes a generic claim. The genus of nucleic acids represents every possible variation which could occur in SEQ ID Nos: 6 and 7, so long as the sequences would hybridize under the stated conditions. In order to provide a representative number of species, in a genus which contains literally hundreds of billions of different members, the court in Lilly required "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. (Lilly at page 1406)." Lilly continues to note that in other cases, two chemical compounds in a subgenus were insufficient to describe that genus. In the current case, Appellant argues that the single species of a

single SEQ ID NO is sufficient to describe other sequence for which no description whatsoever is given. These sequences may be of any size or structure, so long as they hybridize. Applicant's analysis is flawed since there is no expectation in the instant case of insubstantial variation because the functional limitation devolves solely to the ability of the nucleic acid to hybridize. However, hybridization is an inherent capability of nucleic acids, and amplification, in particular, can be achieved with non specific primers. Many methods, ranging from ARMS to differential display, specifically rely on the fact that nonspecific unrelated nucleic acids are capable of amplifying specific targets under conditions of significant stringency. So the argument by Applicant that there would be insubstantial variation is not correct since the function of hybridizing and amplifying does not limit the nucleic acid in any significant way.

Applicant appears to also be making the argument that the size of the genus is not relevant. This is not found persuasive because the size of the genus is a central issue. If the genus were small, a written description rejection would be less likely, since the examples would be more representative of the genus. Here, where the genus includes nearly every possible nucleic acid primer, literally trillions and trillions of possible molecules, none of which are disclosed or taught by Applicant, the argument that the demonstrated species is representative is not found persuasive.

Absence of any structure-function relationship

Second, when Applicant relies upon the analysis of the written description guidelines, this analysis is based upon the assumption that there will be insubstantial variation, as noted in many of the examples including example 9. However, Applicant's

analysis is flawed since there is no expectation in the instant case of insubstantial variation because the functional limitation devolves solely to the ability of the nucleic acid to hybridize. This is not like example 9, where the functional limitation involved a protein which retained adenylate cyclase activity. In the example 9 case, the argument of insubstantial variation was that there was an expectation that stringently hybridizing proteins which retained the specific function of stimulating adenylate cyclase would differ insubstantially. Applicant's fundamental position fails to equate with the written description guidelines because in the guidelines, there is function correlated to the structure. Applicant's claims, however, lack any function whatsoever. So consonant with the case law in Lilly, Enzo and the other written description decision of the Federal Circuit, it is clear that the current claims fail to meet the written description requirement because there is literally no structure whatsoever.

Applicant's conclusion that no more than a single sequence and specific high stringency conditions are required to support a genus claim based upon the guidelines is consequently incorrect. The guidelines require more. They require a structure function relationship.

The claim scope broadly encompasses sequences from other species

Finally, when Applicant argues that the case is different from the issues cited in Lilly and Fiers, Applicant fails to appreciate the breadth of the claim. The current claim clearly reads on sequences found not only in humans, but in other species. This was the crux of the decision in Lilly, that a rat insulin sequence did not provide sufficient breadth to provide descriptive support for a claim which encompassed human insulin

nucleic acid sequences. Applicant's claim suffers from the same flaw, since the claim would clearly encompass sequences from other species. For example, an alignment of nucleotides 105 to 266 of SEQ ID NO: 6 with the mouse Genbank Accession No. XM_218828 shows an 88% alignment with a region of 40 nucleotides in common (with a Tm of 73 C for the 40 nucleotides alone). (This is post filing date art). Now that the claims have conditions which make sense, the claim can be analyzed for hybridization. So the claim as written would encompass a rat sequence, not described by Applicant, which is the express problem raised in Lilly. It is clear that Applicant did not have possession of this sequence, since there was no recognition of the particular changes that would result in the sequence. However,

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Query: 4     cagcagctgctgaccctgcagaaccaggtggcgcggctggaggaggagaaccgagactt- 62
             ||||||||| ||| |||||||| ||| ||||| ||||| |||||||||| ||||||||
Sbjct: 1459 cagcagctgttgatcctgcagagccaagtggcccggctagaggaggagaatcgagacttc 1518

Query: 63    ttggctgcgctggaggacgccatggagcagtacaaactgcagagcgaccggctgcgtgag 122
              ||||  ||  ||||||||||||||||||||||||||||||||||||||||||| ||||| |||
Sbjct: 1519 ctggcggctttggaggacgccatggagcagtacaaactgcagagcgaccgcctgcgggag 1578

Query: 123   cagcaggaggagatggtggaactgcggctgcggttagagctgg 165
             |||||||| |||||||||||||| ||||| ||  |||||||||
Sbjct: 1579 cagcaggaagagatggtggaacttcggctacgcctagagctgg 1621
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So the claims clearly encompass sequences which were neither taught nor described by the current specification. The claims include a single species which is not representative of the full scope of the genus. The guidelines support the rejection, particularly the requirement of Example 9 for a structure function relationship. Therefore, the written description rejection is maintained.

Conclusion

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
1/24/04